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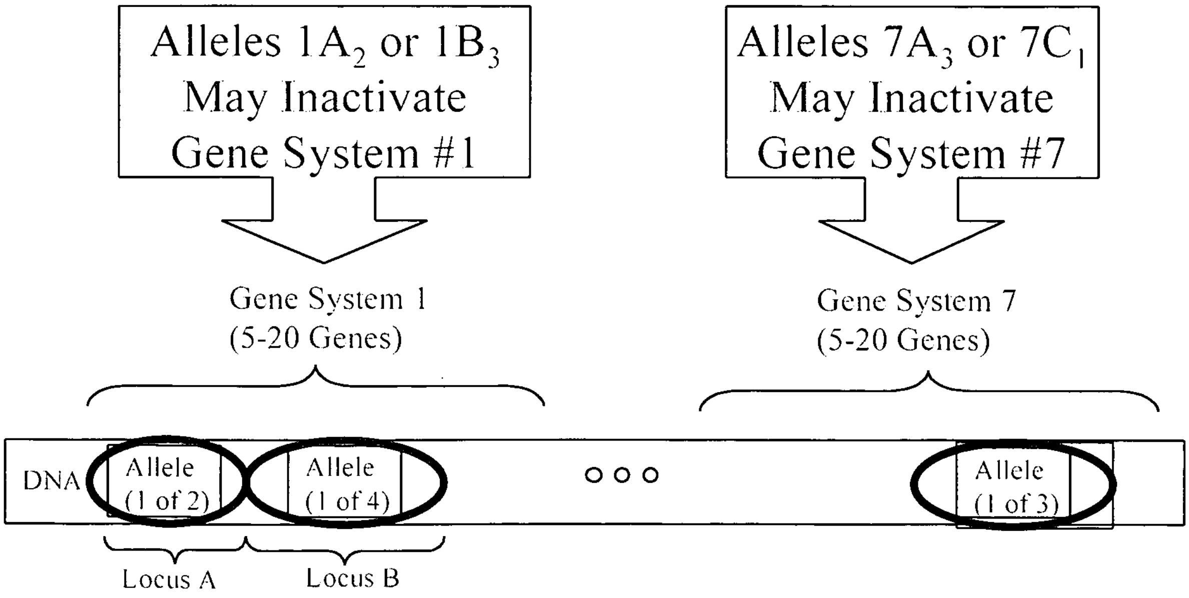
Figure 1A
Identification of Functional Allele Families: Motivation

- ◇ Repetitive Gene Systems
  - o Repetitive Biochemical Functions
  - o E.g. systems 1, 7
- ◇ Both systems must be inactivated before problems
  - o E.g. (($1A_2$ or $1B_3$) and ($7A_3$ or $7C_1$))
  - o Automatic choice of allele combinations required



Alleles $1A_2$ or $1B_3$ May Inactivate Gene System #1

Alleles $7A_3$ or $7C_1$ May Inactivate Gene System #7

Figure 1B
Method of Identifying Clinically Relevant Allele Combinations

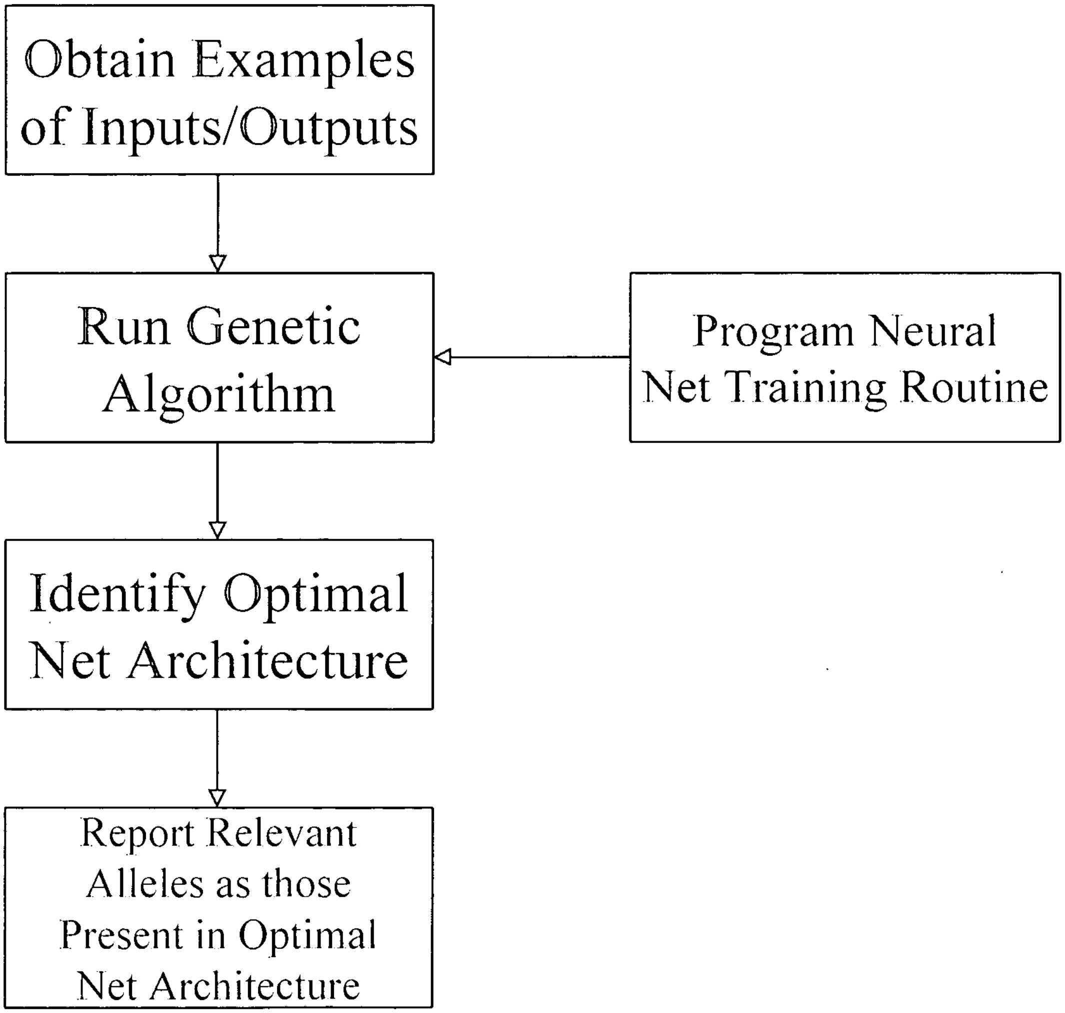

Obtain Examples of Inputs/Outputs
Run Genetic Algorithm
Program Neural Net Training Routine
Identify Optimal Net Architecture
Report Relevant Alleles as those Present in Optimal Net Architecture

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Figure 1C
Structure of Neural Network
Training Routine

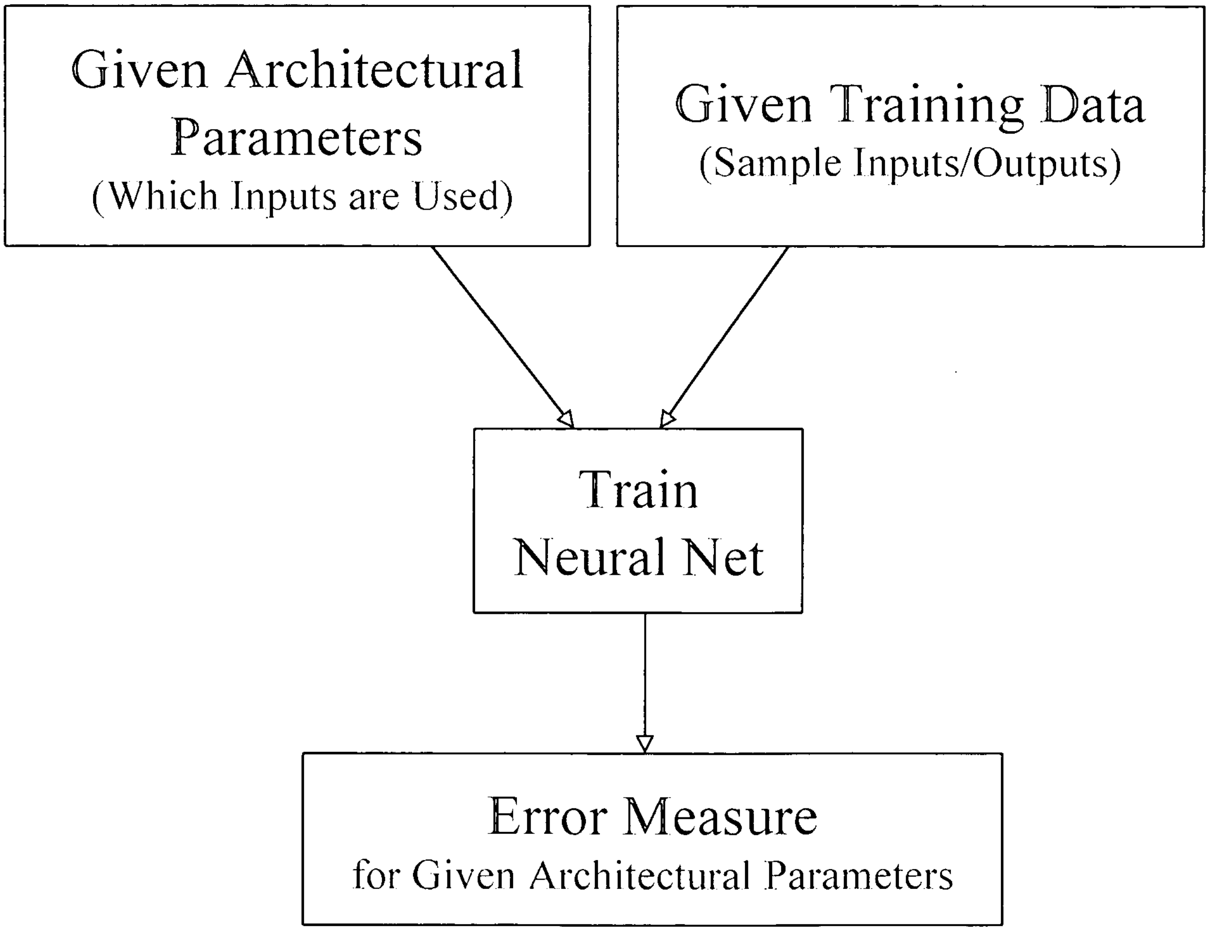

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Figure 1D:

Typical Mapping Neural Network

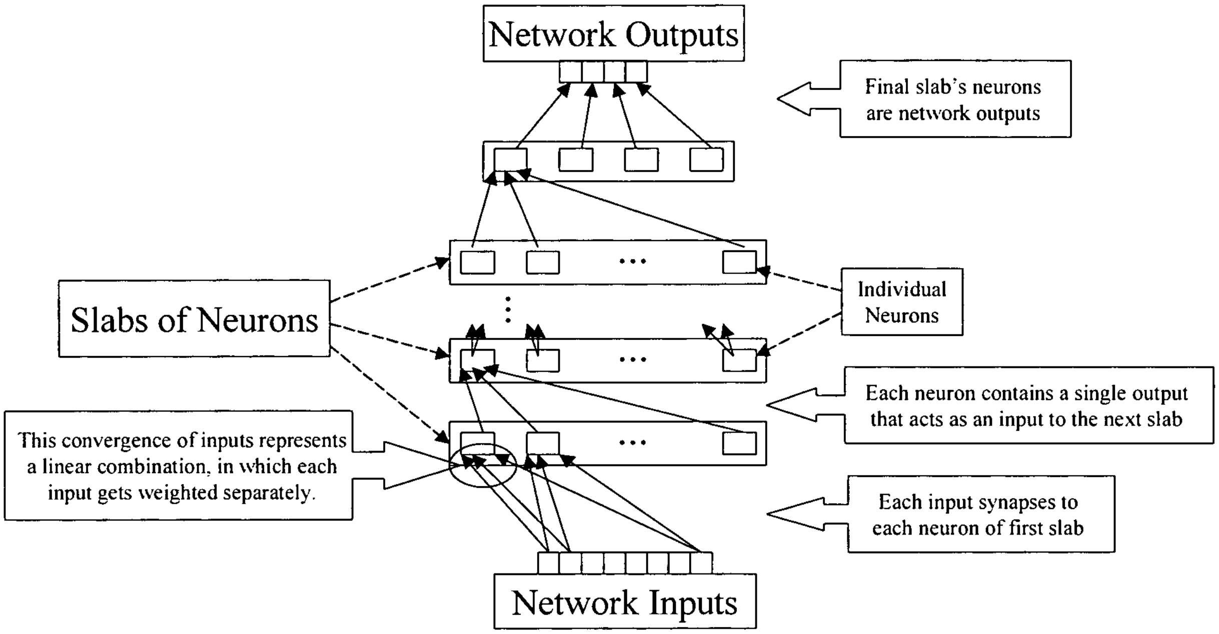
Network Outputs
Final slab's neurons are network outputs
Slabs of Neurons
Individual Neurons
Each neuron contains a single output that acts as an input to the next slab
This convergence of inputs represents a linear combination, in which each input gets weighted separately.
Each input synapses to each neuron of first slab
Network Inputs

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Figure 1E: Typical Genetic Algorithm

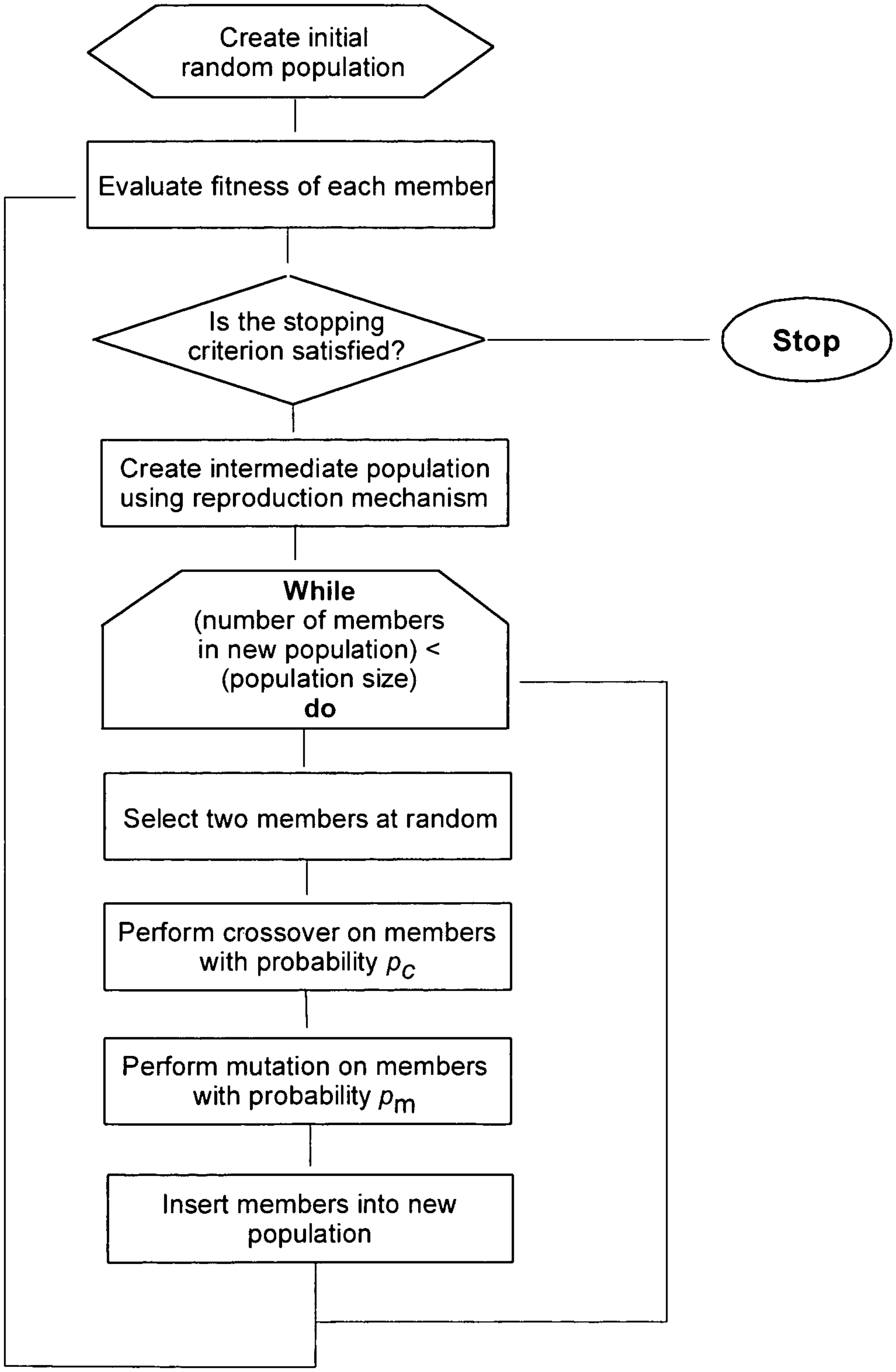
Create initial random population
Evaluate fitness of each member
Is the stopping criterion satisfied?
Stop
Create intermediate population using reproduction mechanism
While (number of members in new population) < (population size) do
Select two members at random
Perform crossover on members with probability p_c
Perform mutation on members with probability p_m
Insert members into new population

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Figure 2
Method of Predicting Clinical Variables
Given Genomic Data

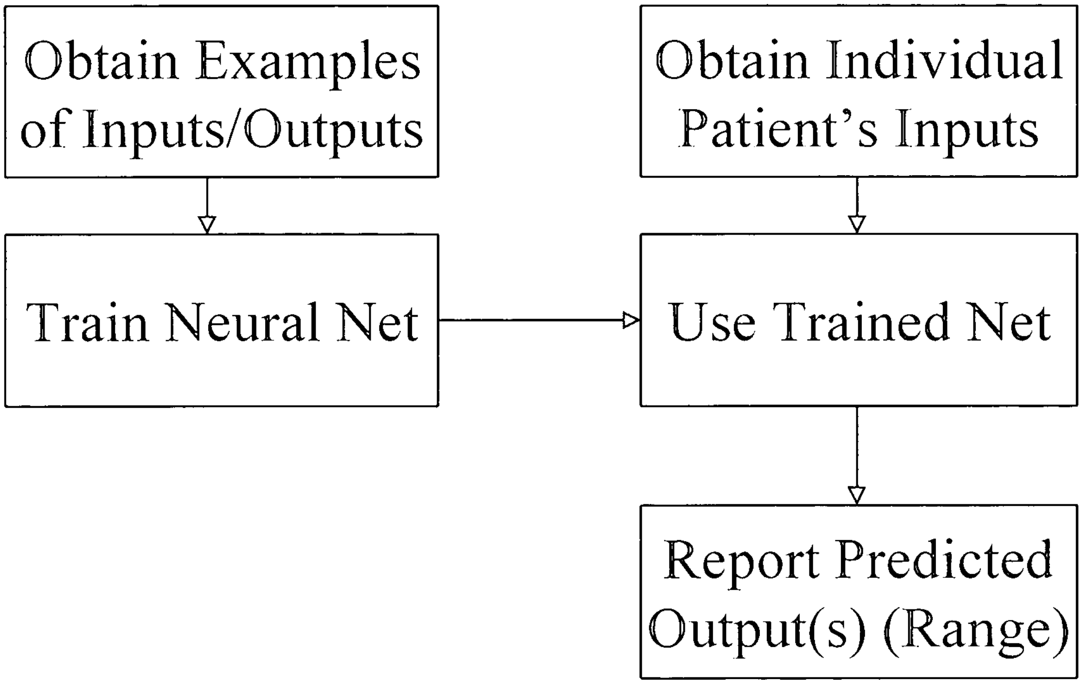
Obtain Examples of Inputs/Outputs
Train Neural Net
Obtain Individual Patient's Inputs
Use Trained Net
Report Predicted Output(s) (Range)

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Figure 3
Genomic Methods of Screening Patients for Clinical Drug Use

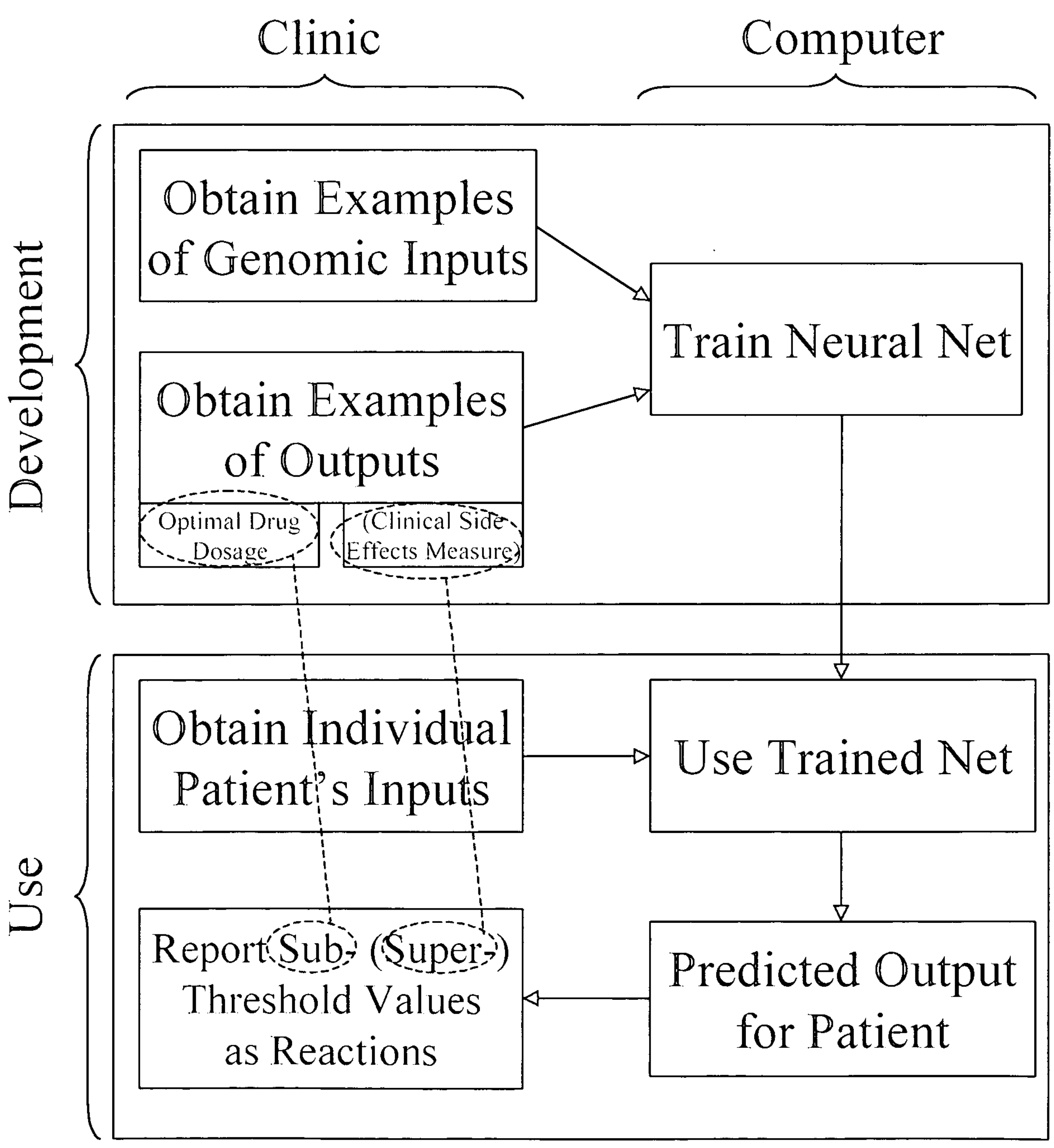
Clinic
Computer
Development
Obtain Examples of Genomic Inputs
Obtain Examples of Outputs
Optimal Drug Dosage
(Clinical Side Effects Measure)
Train Neural Net
Use
Obtain Individual Patient's Inputs
Use Trained Net
Report Sub- (Super-) Threshold Values as Reactions
Predicted Output for Patient

Figure 4A
GA Rolling: Illustration of Infeasible Initial Mapping Problem

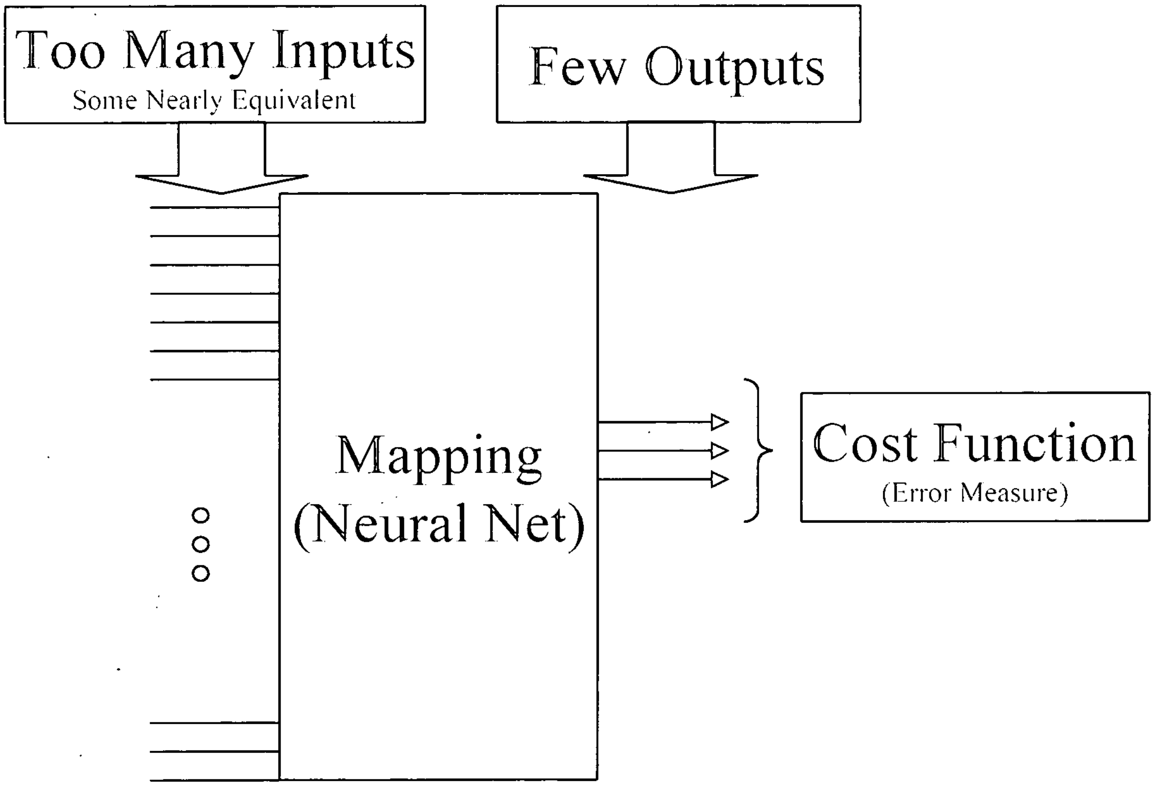

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Figure 4B
GA Rolling: Illustration of Individual Category and its Genes

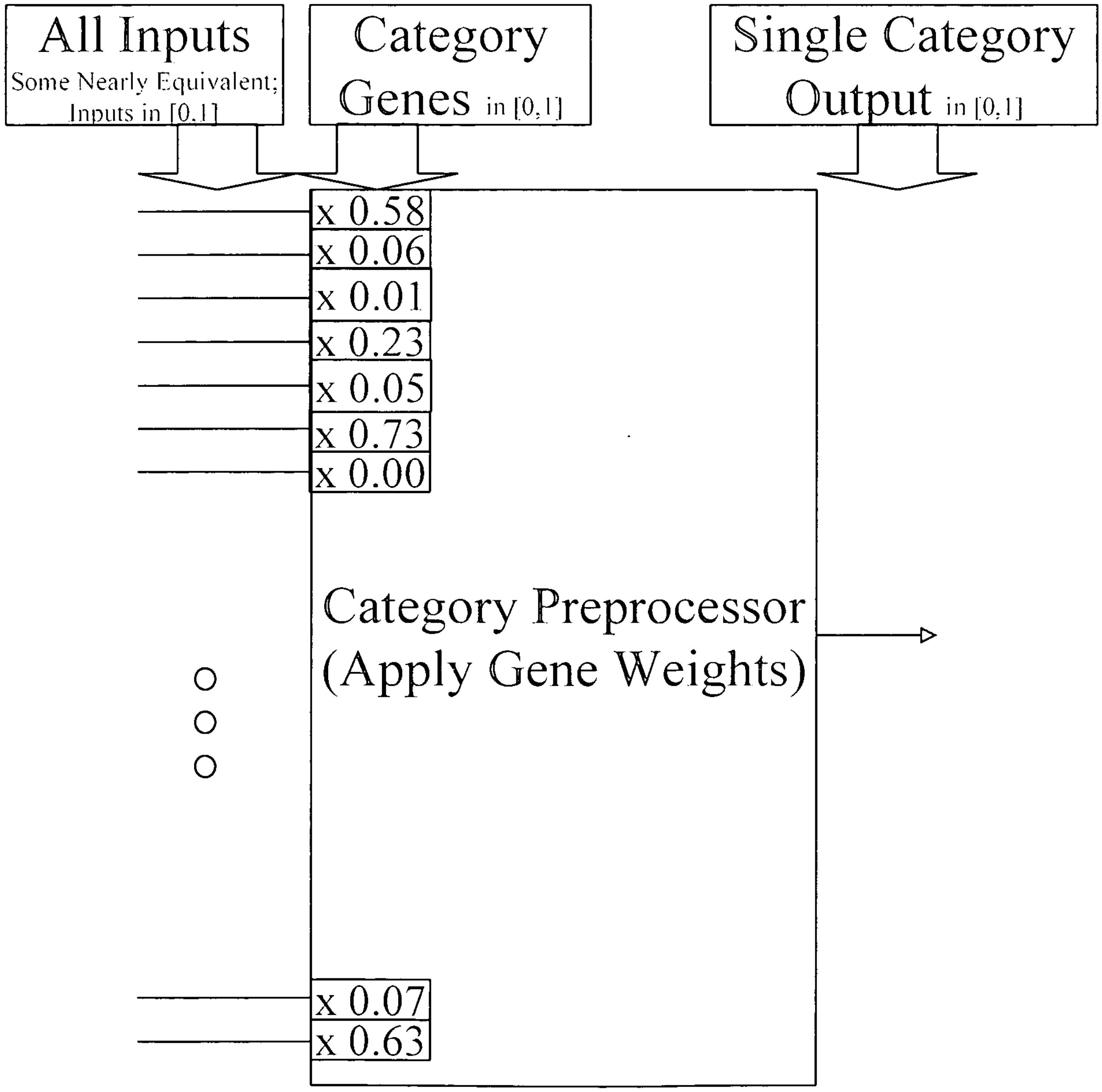

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Figure 4C
GA Rolling: Illustration of the Mapping Used by the Genetic Algorithm

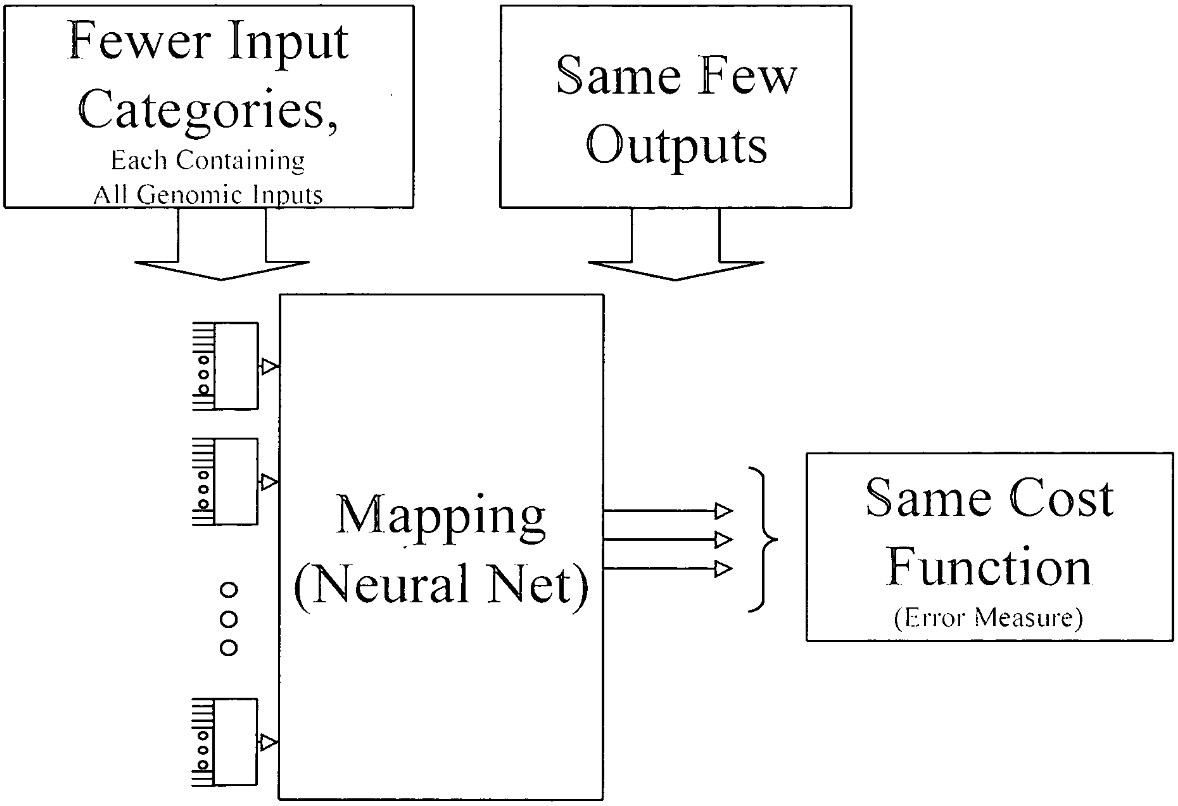

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Figure 4D
GA Rolling: Illustration of the Use of the Genetic Algorithm

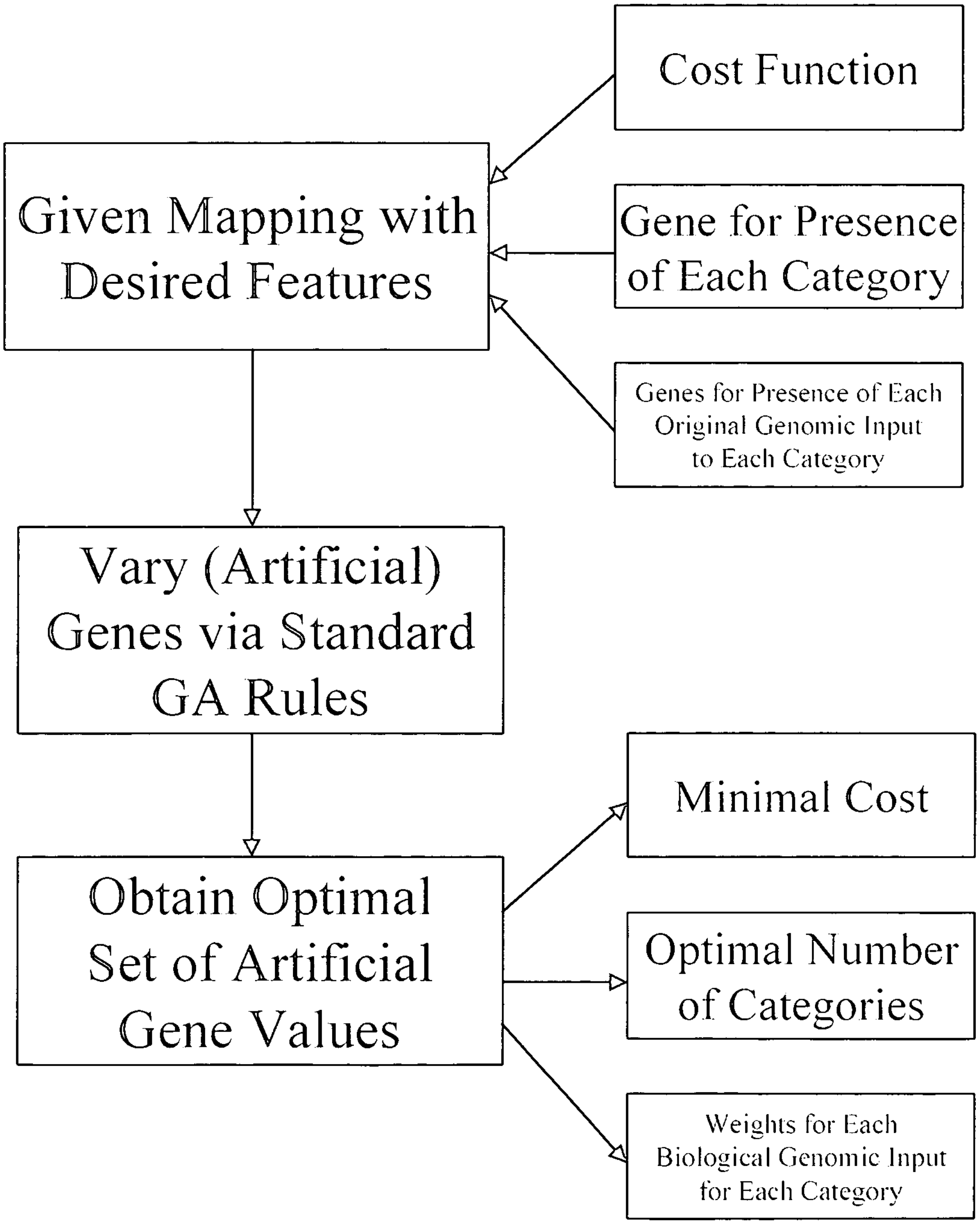
Cost Function
Given Mapping with Desired Features
Gene for Presence of Each Category
Genes for Presence of Each Original Genomic Input to Each Category
Vary (Artificial) Genes via Standard GA Rules
Minimal Cost
Obtain Optimal Set of Artificial Gene Values
Optimal Number of Categories
Weights for Each Biological Genomic Input for Each Category

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Figure 5A
Use of Functional Genomic Categorizations for Predicting Drug Interactions: Preliminary Constructs

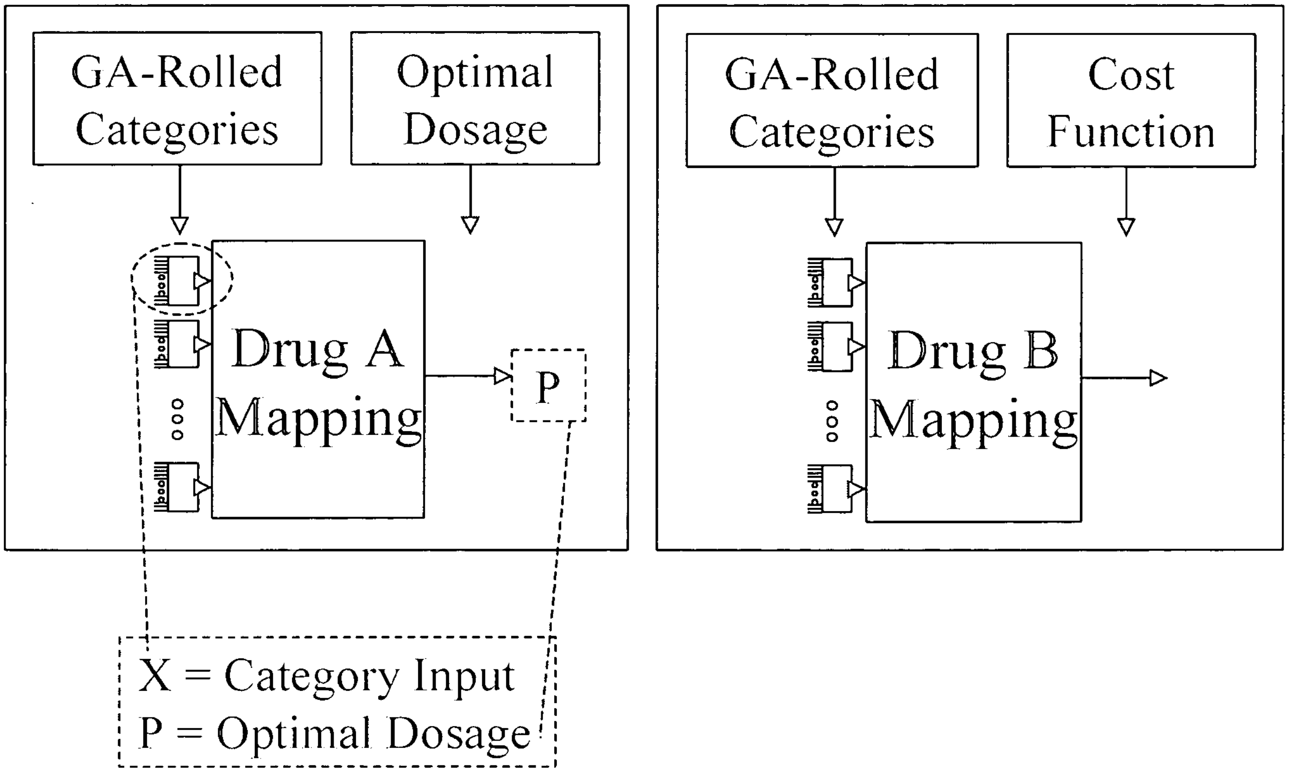
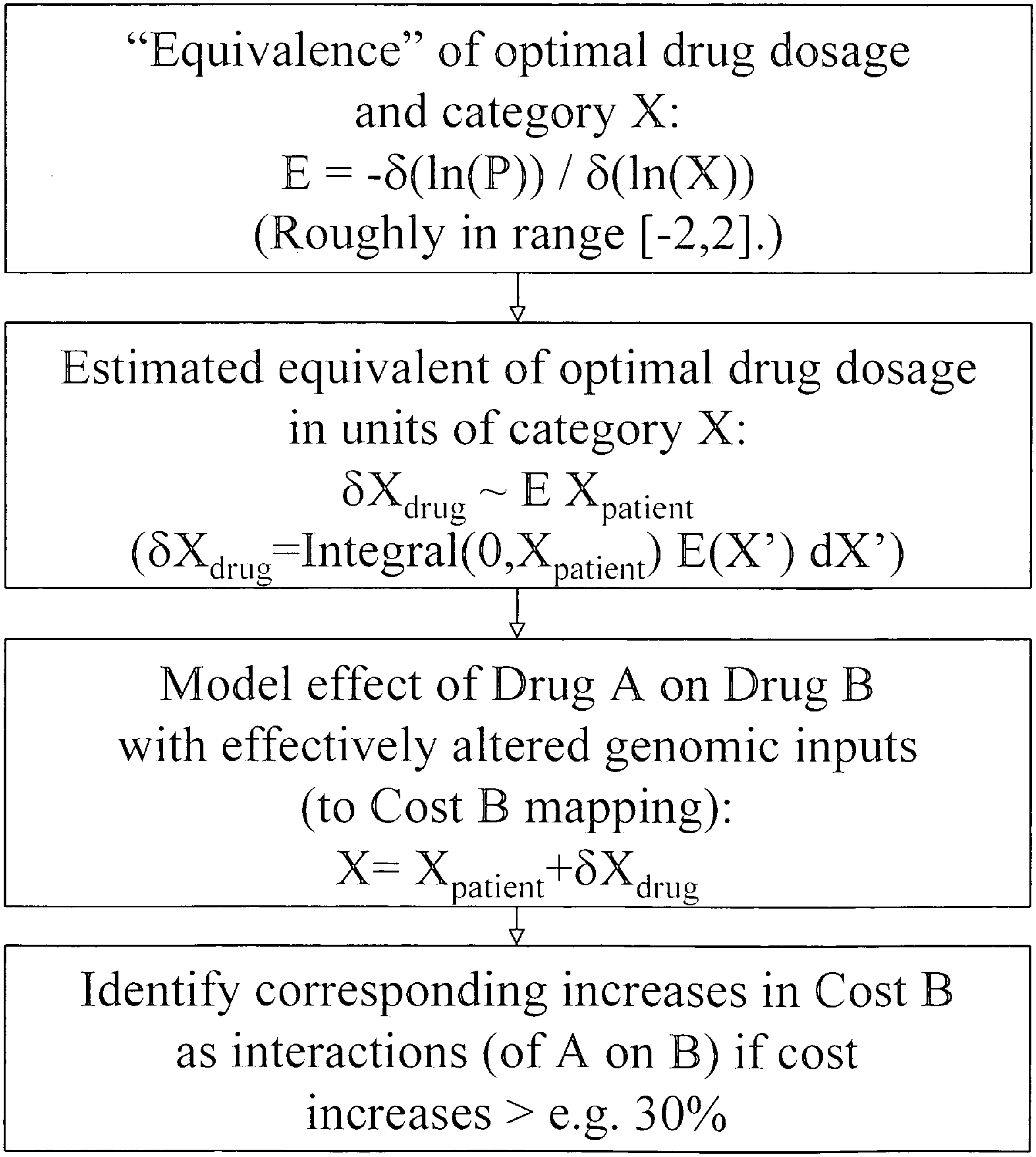


Figure 5B

Use of Functional Genomic Categorizations for Predicting Drug Interactions: Intermediate Calculations



"Equivalence" of optimal drug dosage and category X:

$$E = -\delta(\ln(P)) / \delta(\ln(X))$$

(Roughly in range [-2,2].)

Estimated equivalent of optimal drug dosage in units of category X:

$$\delta X_{drug} \sim E\, X_{patient}$$

$$(\delta X_{drug} = \text{Integral}(0, X_{patient})\ E(X')\ dX')$$

Model effect of Drug A on Drug B with effectively altered genomic inputs (to Cost B mapping):

$$X = X_{patient} + \delta X_{drug}$$

Identify corresponding increases in Cost B as interactions (of A on B) if cost increases > e.g. 30%

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Figure 6A
Universal Functional Genomic Categorization:
Assembly of Categories

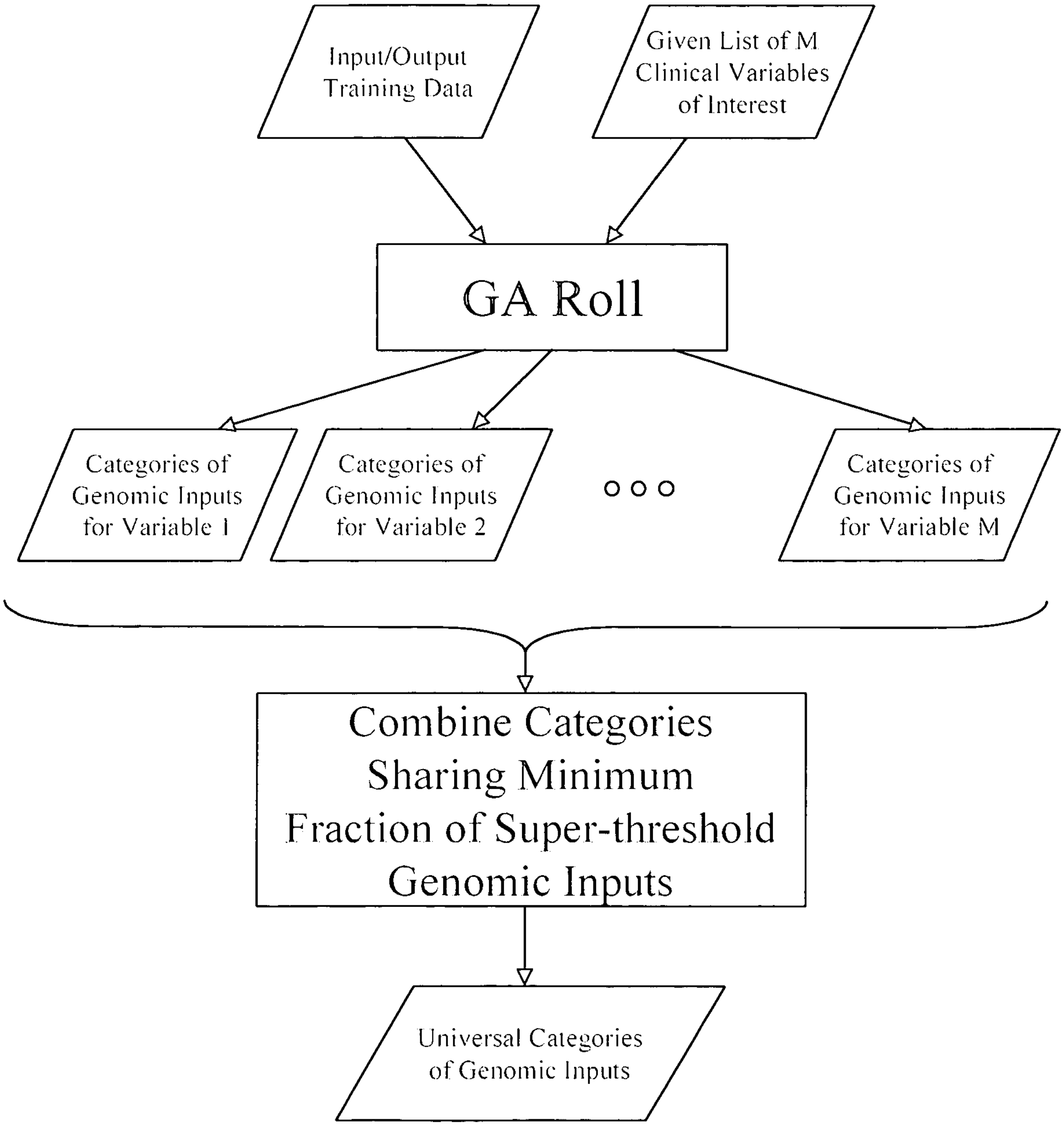
Input/Output Training Data
Given List of M Clinical Variables of Interest
GA Roll
Categories of Genomic Inputs for Variable 1
Categories of Genomic Inputs for Variable 2
○ ○ ○
Categories of Genomic Inputs for Variable M
Combine Categories Sharing Minimum Fraction of Super-threshold Genomic Inputs
Universal Categories of Genomic Inputs

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Figure 6B
Universal Functional Genomic Categorization: Calculation of Probabilities: Given Information

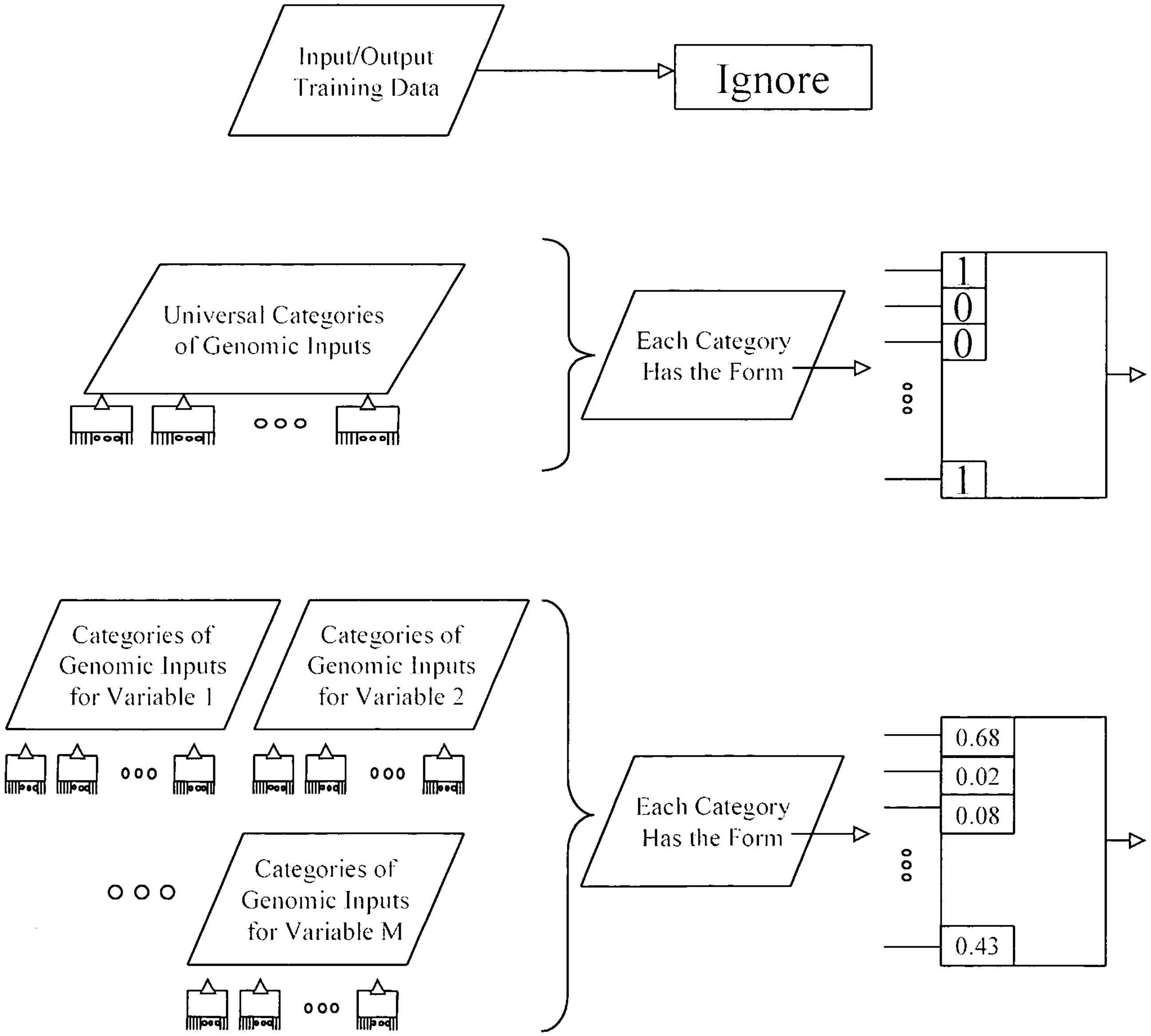
Input/Output Training Data
Ignore
Universal Categories of Genomic Inputs
Each Category Has the Form
1
0
0
1
Categories of Genomic Inputs for Variable 1
Categories of Genomic Inputs for Variable 2
Categories of Genomic Inputs for Variable M
Each Category Has the Form
0.68
0.02
0.08
0.43

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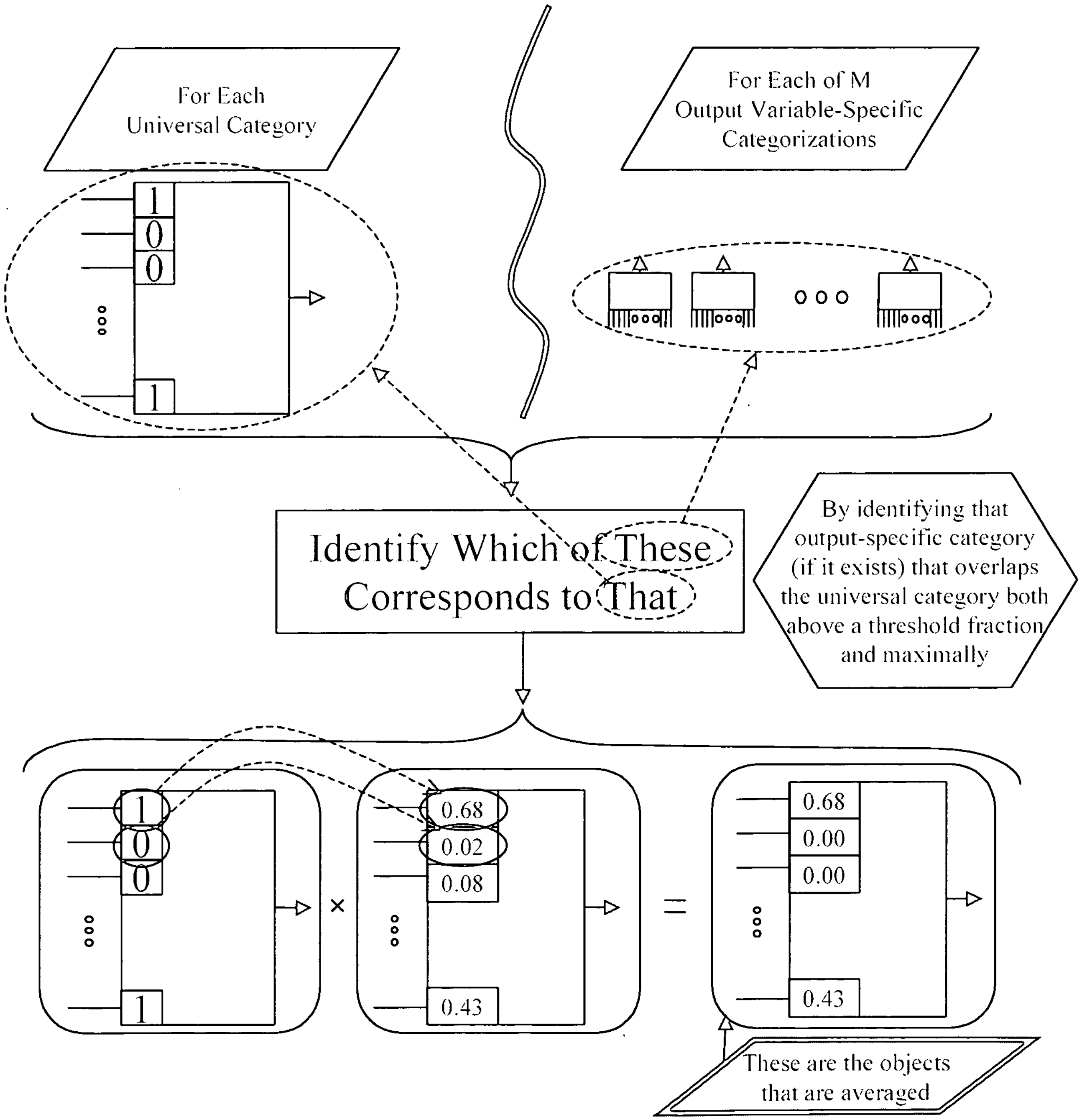
Figure 6C

Universal Functional Genomic Categorization: Calculation of Probabilities: Identification of Data


For Each Universal Category
For Each of M Output Variable-Specific Categorizations
1
0
0
1
Identify Which of These Corresponds to That
By identifying that output-specific category (if it exists) that overlaps the universal category both above a threshold fraction and maximally
1
0
0
1
×
0.68
0.02
0.08
0.43
=
0.68
0.00
0.00
0.43
These are the objects that are averaged